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A NEUROPATHOLOGICAL STUDY OF "YOSHIDA SARCOMA"

by

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I. INTRODUCTION

It is well known that sarcoma, "a malignant neoplasma", is a particular tissue of pathological nature which originates in preexistent cells of the living body, with endless automaticity of growth which endangers life. This fact is evident in clinical course of the patient and shows the nature of the sarcoma. There is an interesting problem about the nerve tissues of the tumor in its autonomous growth, about which many discussions but few conclusions have occurred. There are many theories concerning this problem, such as, the negative theory which denies the existence of nerve tissue in the tumor, the neoplastic or productive theory which recognizes production of nerve tissue in the tumor, the destructive theory which insists that there is destruction of nerve tissue in the tumor. However none of them has yet given any confirmatory evidence to date.

In a study of the nerve tissues in sarcoma it is difficult to clarify many factors if only human sarcoma is studied, because the specimens of human sarcoma cannot be taken out of an organ at a particular stage of growth as desired. Threfore it is necessary to work out a complete systematic study using experimental tumors.

This is a report of a histological study of nerve tissue in the growth process of YOSHIDA sarcoma which is an implant-sarcoma of rats.

II. PROCEDURE

Rats weighing 80-120 grams are used and after through observation of normal nerve tissue a comparison of the nerve tissues of Yoshida sarcoma and of abnormal nerve tissue affected by experimental neurotomy or injection of drugs will be made.

Procedures are as follows. After fixation of the tissues in 10% neutral formol solution for 2 months, frozen sections are cut and stored in 10% neutral formol solution for more than a month. SETO's variation of BIERSCHOWSKY's neuro-axis silver stain and EHRLICH's acid hematoxylin myelinsheath staining are used.

1. YOSHIDA sarcoma

Stem: TAKEDA YAKKO. G-114

Implantation: With a capillary pipette made of glass tube of 7 mm diameter, 0,05-0,1 cc of ascites were aspirated by means of capillary action from the abdominal

cavity of a rat 4 or 5 days after implantation, and injected into the abdominal cavity or the subcutaneous tissue of a normal rat. Thus the sarcoma of ascites type or subcutaneous tissue type were obtained. (The nomenclature of ascites type or subcutaneous tissue type will be used in all successive articles.)

2. Control

1) Experimental nerve degeneration due to neurotomy

After cutting the ischiadicus nerve at the root, preparations were made from the peripheral region at intervals of 2, 3, 4, 5, 6, 7, 8 and 14 days, and nerve degeneration observed in each specimen.

2) Experimental nerve degeneration due to drug injection

After injection of alcohol or phenol at the root of ischiadicus nerve, the same procedures as above were repeated. The alcohol used in this experiment were in concentrations of pure, 80%, 60% and 40% and the phenol were 10%, 8%, 4% and 2%.

III. RESULTS

1. The infiltration of Yoshida sarcoma in rats.

1) Ascites type

4 to 6 cc thick, white turbid or slightly, "tumor like" ascites was observed in the abdominal cavity. In the male animal, the surrounding tissue of the testis was changed into a whitish elastic and relatively soft tumor tissue, and the testis was buried in tumor though the original shape was retained. The tumor extended diffusely into the spermatic duct, prostate, seminal vesicle, and then to the perirectal and retroperitoneal connective tissues. In the female, the tumor tissues infiltrated the surrounding tissue of the uterus and ovaries. The uterine wall at the corner was intensively thickened by tumor infiltration. The tumor reached to the perirenal area through the subserous tissue of the lower abdomen and pelvic cavity. The infiltrated part was white or partially brown in color and swollen with soft tissue, but never formed a localized tumor mass.

The mesentery was thickened in general but the superficial serous membrane retained its normal appearance. In some parts the tumor cells penetrated through the mesentery to the intestine wall. In greater omentum was markedly thickened by tumor cell infiltration. The pancreas was also completely buried involved by the tumor. Generally speaking, it is a peculiarity of this type of tumor that the original form of the organ is well preserved even with a diffuse infiltration of tumor cells.

In liver and spleen a marked tumor infiltration was noted around the hilar areas, and the tumor cells penetrated and extended along the bile ducts or the blood vessels but never broke through the serous membrane. The tumor cells infiltrated the wall of the extrahepatic bile ducts and formed a tumor mass involving the lesser omentum.

Frequently in the kidney the tumor cells penetrated the cortical surface. Cells infiltrating the retroperitoneal tissue go through the part of the kidney covered by

serous membrane.

In animals surviving for long periods of time, the tumor cells pierced all layers of the diaphragm and caused pleural exudation. No pulmonary metastases were seen in cases of the ascites type. However, after pleural involvement the tumor penetrated into the lung along the course of the bronchi.

2.) Subcutaneous tissue form

In this form the neoplasm is not so strongly infiltrative but make a localized ball-like tumor which is covered with a somewhat fibrous membrane, though some of these cases show the presence of white colored ascites in the end stage. Sometimes metastasis in kidney, lung and intestine tract were noted but usually the metastasis was not so severe in comparison to that of the ascites type. The life span of animals with the subcutaneous tissue type was longer than that of the ascites type by 10 to 20 days. Therefore, at time of making preparations, some organ in the subcutaneous tissue type showed more infiltration of tumor cells than in ascites type.

2. Microscopic findings

1) Yoshida sarcoma

Microscopic observations were made on selected tissues or organs where the tumor infiltration was seen to be intensive and sampling was thought to be relatively easy.

A. Lung

In general no lung metastasis was seen in animals with the ascites type but early lung metastasis was noted in the cases with pleural involvement. Microscopic study of these cases revealed that the tumor cells which extended along the course of bronchi from the hilum extended to the peripheral part of the lung though the degree of infiltration was not so severe.

Normally almost all of the nerve fibers from the plexus pulmonalis located at the pulmonal hilum run along the bronchi and the rest along the blood vessels to the peripheral parts of the lung, and the nerve fibers which go along the bronchi chiefly consist of myelinated nerve fibers, with few ganglion cells interspersed. Though a large part of these nerve bundles showed normal finding, a clear-cut degeneration was noted here and there probably due to penetration by tumor cells. This degeneration consisted of swelling of axis-cylinders to the form of sausages or spindles with vacuoles inside. (Fig. 1) The same sort of degeneration with swelling or vacuole formation was seen in myelin sheaths though the degree is not so severe. Normal nerve plexus, which is composed of many non-mylinated and a few myelinated nerve fibers, in orderly pattern was observed in the bronchial submucous tissue where scanty tumor infiltration was seen.

In animals with the subcutaneous tissue type, no pulmonary metastasis was observed except in one rat that died 15 days after implantation following development of a few area of tumorous pleural exsudate. In the microscopic observation of this case it was noted that the tumor cells extended to the periphery of the lung along the course of bronchi, partially penetrating the bronchial muscle layer as far

as the submucous tissue. The nerve bundles located along the bronchi in the hilum were severely degenerated and destroyed by tumor infiltration. Part of the axis-cylinders were broken down to irregular granules, and in other parts they were swollen to sausage or spindle forms with vacuole formation. The affinity to silver also varied from hypersensitive. (Fig. 2, 3) The myelin sheaths were also markedly destroyed and heavily swollen containing many vacuoles. (Fig. 4, 5) The tumor infiltration in the submucous tissues was so intensive that the nerve plexus composed of fine nerve fibers completely disappeared.

B. Stomach

Greater and lesser omentum of animals with the ascites type were markedly thickened by tumor infiltration. In this case the tumor cells invaded the gastric serous membrane from the attachment of both omenta to the stomach, and penetrated partially to the muscle layer. Many groups of myelinated and non-myelinated nerve fibers and several groups of ganglion cells were found at the attachment of the lesser omentum to the stomach. In some parts, the course of these nerve bundles was indistinct and fibers become coarse, and in other parts the axis-cylinders were irregularly swollen, and showed the decreased affinity for silver stains. These findings show a clear-cut picture of degeneration of the nervous system. (Fig. 6)

It was somewhat difficult to find the AUERBACH's plexus because of its location between the external longitudinal muscle layer and circular muscle layer of the stomach. In general, the tumor cells infiltrated the external layer of longitudinal muscles but hardly reached the layer of internal circular muscles. Therefore, no tumor infiltration was found in the region of AUERBACH's plexus. The nerve fibers of the plexus were divided into branches and at the junction of the fibers many ganglion cells were observed. (Fig. 8) Some nerve fibers were enlarged into club shapes, (Fig. 7), and hyperchromasia, which is a sign of early degeneration was noted, but almost all nerve fibers and ganglion cells are retained their normal contour.

No effect of tumor infiltration was seen in MEISSNER's plexus. The fine nerve fibers were quite orderly and showed normal reticuli. Thus the finding of "Schlaengend Territorie" named by STOEHR remained normal. (Fig. 9)

C. Small intestine

In the animals with the ascites type, the mesenterium was markedly swollen and microscopically the tumor infiltration was found to penetrate the subserous membrane to the intestine wall, and finally the serous membrane showed desquamation. In other cases the tumor infiltrated the submucous membrane through the muscle layer at the attachent of the mesentery to the intestinal wall.

Like the nervous mechanism of the small intestine, AUERBACH's plexus which is located between the longitudinal muscle and circular layers, and MEISSNER's plexus which is located in submucous membrane are known. Those plexuses were both highly affected by tumor infiltration in the case of the YOSHIDA sarcoma. In general, the ganglion cells of AUERBACH's plexus were hyperchromatic to silver and the cellular border became indistinct. Also the ganglion cells were reduced in number, and most of them were lacking in axis-cylinder processes. In some part, there were

wide spaces between the ganglion cells and the bodies of the accessory cells in accordance with atrophy of ganglion cell bodies. (Fig. 10) In other parts the cytoplasm of ganglion cells was destroyed, and as a result, only the nuclear shadows or the nuclei of the accessory cells were retained. In some cases the granular degeneration or vacuole formation in cytoplasm of ganglion cells was observed. (Fig. 11) In accordance with this degeneration in cytoplasm of ganglion cells, the nuclei also disintegrated, i. e. were small in size, irregular in shape (wave-like, serrated), or hyperchromatic to silver stains. (Fig. 12, 13) The nerve fibers were markedly reduced in number or partially disappeared at the region where the infiltration of tumor cells was most intensive. In the region where infiltration was slight, quite a few nerve fibers remained but showed partial granular degeneration, i. e. the nerve fibers were disintegrated into granular substance. (Fig. 14, 15) In some parts, changes suggestive of granular degeneration of nervous syncytium were present.

Almost the same degeneration seen in AUERBACH's plexus was observed in MEISSNER's plexus when the tumor infiltration reached the submucous layer. There was a reduction of the ganglion cell count, loss of axis-cylinder processes, and widened spaces between the nerve cells and bodies of the accessory cells due to atrophy of the ganglion cell bodies. Along with this atrophy of the cell bodies cellular destruction was also noted. The nuclei were all pyknotic, concentrated and irregular in shape. (Fig. 16) The nerve fibers were reduced in number and in some places had completely disappeared. However, in the uninvolved sections of the intestine where the tumor infiltration had stopped at the muscle layer and no infiltration was observed in the submucous layer, the nervous mechanism remained essentially. (Fig. 18)

In the intestines of normal animals many terminal reticuli (STOEHR) or nervous syncytia (Jabonero) which are the terminal element of the autonomic nervous system of intestine noted. However, almost no such elements were seen in animals with implanted sarcoma either in highly infiltrated parts of intestine or in parts with slight in filtration by tumor cells. The only exception which showed a granular degeneration of the terminal elements in a region slightly infiltrated by tumor cells was observed as shown in Fig. 17.

D. Rectum

In animals with the ascites type of tumor, it is observed that the tumor cells infiltrated from a region of rectum where the serous membrane was lacking into the submucous tissue through the muscle layer.

The ganglion cells and the nerve fibers in the rectal nervous mechanism were markedly degenerated by tumor infiltration, reduced in number, in some areas and missing in other areas. Almost all of the ganglion cells lost their original shape and were deformed into long narrow cells or only nuclear shadows without cytoplasm. The nuclei showed pykosis or were occasionally deformed into long nuclei. (Fig. 19, 20) The nerve fibers were also reduced in number, deformed and in some areas only traces could be found.

In MEISSNER's nervous plexus the same findings of atrophy or degeneration as

mentioned above was observed. The nerve fibers occasionally present only in traces.

No nervous syncytium was seen in rectum.

E. Liver and bile duct

In animals with the ascites type of tumor, the infiltration of tumor cells was most intensive in the portal area and this infiltration advanced into the liver along the bile ducts or vessels, and produced tumor foci of various sizes in GLISSON's capsule or in liver acini. At the same time an intensive infiltration of tumor cells into the wall of the extrahepatic bile ducts or destruction of the intrahepatic bile ducts due to the infiltration was observed.

The nerve bundles normally originate from the hepatic plexus which is located in the region of the hepatic artery, and pass into the liver along the artery through the hepatic hilum. The nerve bundles at the hepatic hilum were markedly degenerated due to intensive infiltration by tumor cells. The axis-cylinders were disintegrated into many granules with irregular shapes, or in some parts, markedly swollen into irregular shapes containing many vacuoles of various sizes. (Fig. 21) The myelin sheaths were also markedly swollen with many vacuoles and were seen as multiple granules which showed affinity to hematoxylin because of qualitative change of chromatin. (Fig. 22)

In the liver, a slight proliferation of tumor cells in GLISSON's capsule was observed, but the nerve fibers were orderly. Considerable degeneration of only a few nerve fibers in the intrahepatic region close to the hilum was noted, where tumor infiltration was marked. (Fig. 23) Many nervous syncytia are seen in GLISSON's capsule of normal animals (Fig. 25), but in the case of implanted tumor no nervous syncytia were observed in parts with tumor infiltration.

F. Abdominal wall

In animals with the ascites type, the tumor grew at the point where the abdominal puncture was done and spread into the muscle layer of the abdominal wall passing through the retroperitoneal tissue so that the muscle fibers in this region were separated into fine fractions. Consequently the infiltration of tumor cells reached the branches of the intercostal nerves.

The nerve bundles in the abdominal wall showed relatively regular lining at the peripheral part of the tumor formation, but close to the center the lining became irregular. The nerve fibers in this region were sometimes definitely degenerated, i. e. the axis-cylinders were degenerated into granules as seen in ordinary granular degeneration or partially into swollen fractions of sausage-shaped forms or spindle forms with vacuoles in them. (Fig. 26) But in other cases a particular finding of axis-cylinder change into a concentration of many small granules with a round, relatively regular shape was observed. (Fig. 28, 29) These findings were more marked at the center of the tumor infiltration than in the peripheral part. In every case the myelin sheath was markedly swollen and contained vacuoles with the affinity to dye being changed, the fine granules being stained by hematoxylin. (Fig. 27, 30)

G. Retroperitoneal muscle

In animals with the ascites tumor, a continuous and wide proliferation of tumor cells in subserous tissue, begining in the pelvic cavity was noted, and the same tumor infiltration in stroma of the retroperitoneal muscle fibers was observed. The nerve fibers running in the stroma clearly showed typical granular degeneration, and the axis-cylinders were deformed into granules of various sizes, which were deeply stained showed partial vacuole formation. (Fig. 31, 32)

H. Suprarenal glands

In animals with the ascites type, the infiltration of tumor cells was very intensive around the suprarenal gland so that it appeared to be surrounded by tumor cells. The tumor cells partially penetrated the zona glomerulosa through the covering membrane.

This gland is normally innervated by both myelinated and non-myelinated nerve fibers which make a nerve bundle, and most of these bundles run into the medulla along the course of the vessels, though others run directly through the covering membrane into the medulla. No tumor infiltration was observed in the zona fasciculata in the suprarenal cortex but the nerve fibers in this layer showed partial granular degeneration, i. e. the axis-cylinders were deformed into irregular shapes and broken into deeply-stained granules. (Fig. 33) There are many nervous mechanism in the medulla such as myelinated fibers, non-myelinated nerve fibers, ganglion cell (Fig. 34), chromaffine cells (Fig. 35) and so on, but none of these showed the presence of tumor infiltration.

I. Kidney

In animals with the ascites type of tumor, the tumor infiltrated from the lower abdomen to the perirenal area continuously through the subserous layer and the most marked infiltration was noted at the renal hilum. Furthermore, the tumor extended into the renal medulla along the course of renal vessels. It partially reached the renal cortex penetrating through the part of the kidneys not covered by serous membrane, but the grade was not so severe. The same sort of tumor infiltration was observed in animals with the subcutaneous type of tumor.

Ordinarily around the renal vessels the renal plexus is located and one or two ganglions are present. The nerve fibers of the renal plexus are composed of myelinated and non-myelinated fibers and run into the kidney along the course of vessels. The nerve fibers in renal parenchyma pass with interlobar arteries to vasa afferentia and efferentia and some of them surround BOWMANN's capsule. Also in the wall of the pelvis renalis and calix renalis many myelinated and non-myelinated nerve fibers are seen.

In animals with the ascites type of tumor, the tumor infiltration was predominant in the region of the renal plexus and a marked change in the renal plexus was noted. In some ganglion cells of this plexus the "Fortsatz-dysharmonie" noted by Stoehr was present. That showed the pattern of irregular processes of ganglion cells or bundle formation of processes from a particular part of ganglion cell. (Fig. 36) On the other hand, so-called "Randstellung der Kern" by FEYRTER which involves eccentric localisation of nuclei in ganglion-cell was also noted. Fig. (37, 38) However,

there were many normal ganglion cells, and those changes in ganglion cells mentioned above were mostly seen in ganglion cells located among the nerve fibers rather than in the ganglion itself. A clear-cut degeneration of nerve fibers in renal plexus was noted. That is, axis-cylinders in the nerve bundles were deformed into irregular shapes and broken into deeply stained granules (Fig. 39) and partially swollen into spindle forms with vacuole formation. (Fig. 40) The myelin sheaths were also swollen and contained many vacuoles. (Fig. 41, 42) Some nerve fibers in the nerve bundle which run into the kidney along the blood vessels showed granular degeneration at the renal hilum. (Fig. 43) The axis-cylinder was also swollen and showed vacuole formation. (Fig. 44)

The majority of nerve bundles which ran along the renal interlobar arteries were normal but in some cases a few of these nerve fibers showed granular degeneration without notable tumor infiltration around the interlobar arteries. (Fig. 45) The nerve fibers which ran along the course of arteria arciformis and arteria interlobularis in kidney were noted to be normal. (Fig. 47) In some cases the uriniferous tubules and vessels in the renal cortex were partially damaged showing loss of their own structure by tumor infiltration, and in these parts, the nervous apparatus was also destroyed and had disappeared.

In animals with subcutaneous type of tumor, the nerve fibers in the pelvis renalis where the tumor infiltration was so intensive fall in granular degeneration, (Fig. 46), but scanty degeneration was seen in the intrinsic nerve fibers of the medulla and renal cortex.

The nervous syncytium is observed in large amount in the pelvis and calix renalis of normal animals, (Fig. 48), but no nervous syncytium was seen in the part damaged by tumor infiltration.

J. Spermatic duct

In animals with the ascites type of tumor, the spermatic duct and its surrounding connective tissues were swollen as a soft tumor mass due to wide, continous tumor infiltration in the subserous tissues. The tumor infiltration reached the tunica muscularis through the tunica adventia and partially to the tunica propria of the spermatic duct.

In some of the nerve fibers such as in the plexus deferentia which runs along the spermatic duct and plexus spermatica which runs along the spermatic artery, fine granular degeneration of axis-cylinder similar to that which occured in the abdominal wall was noted. There was degeneration of axis-cylinders into numerous round, fine granules. (Fig. 49) And in other cases swelling of axis-cylinders into spindle forms or vacuole formation was noted. (Fig. 50)

2) Experimental degeneration of nerve fibers by neurotomy or application of alcohol

A) Degeneration of peripheral ischiadicus nerve after neurotomy (WALLER'S degeneration) and its chronological process

2 days after neurotomy, the nerve fibers had already begun swelling, i. e. axis-cylinders and myelin sheaths were slightly swollen and many granules with affinity

for hematoxylin were seen. At this time the degeneration of myelin sheaths was firstly noted and at the point of RANVIER's node and then extending in thick nerve. (Fig. 51, 52)

The swelling increased on the third day. The axis-cylinders and the myelin sheaths were both irregularly swollen, many vacuoles were formed in them, and some of them were damaged into elliptical or round granules. Also, it was observed that the SCHWANN's cells were elongated and string like among the nerve fibers.

In a stage of further degeneration 4 or 5 days after the neurotomy the axis-cylinders were changed into granules and many types vacuoles were present in them. The affinity to silver was somewhat increased. The myelin sheaths were broken into drop-like pieces of various sizes and many of these various vacuoles were present in them. (Fig. 53, 54)

6 to 8 days after the neurotomy the grade of degeneration had reached its maximum and all of the axis-cylinders and myelin sheaths lost their original form, and the above stated granules were further broken into many fine pieces and many vacuoles were present in them. (Fig. 55, 56, 57, 58)

14 days after the neurotomy a clearing of the degenerated field was noted and the number of fine granules was reduced by absorption although a few still remained. On the other hand it was remarkable that the SCHWANN's cellular nuclei had thickend and increased in number. (Fig. 59, 60)

B) Degeneration of ischiadicus nerve after application of druge injection and its chronological process

The medicines used for this experiment were alcohol of absolute, 80%, 60% and 40% and phenol of 10%, 8%, 6% and 4%. There was no significant differences between the various concentrations of these medicines, so as an example, the examination of the degenerative process of nerve using absolute alcohol application will be described.

2 days after injection the degenerative process started and the axis-cylinders and myelin sheath of nerve fibers were slightly swollen.

4 days later irregular swellings and vacuole formation in various parts of the axis-cylinders were noted and some of them were already broken into many granules, the myelin sheath also showing the same sort of degeneration. This process of degeneration also started at the point of RANVIER's nodes as seen in WALLER's degeneration. (Fig. 61)

6 or 8 days after injection a typical degeneration pattern with rosary formation was observed. This involved the breakdown of axis-cylinder and myelin sheaths into chains of small pieces. In each piece many vacuoles were present, especially at the stage of maximum degeneration. (Fig. 62)

14 days later clearing of the degenerated field was noted and a few of the degenerated substances remained, and SCHWANN's cells were thickened and increased in number (Fig. 63).

IIII. DISCUSSION

Pathologists long have been interested in the problem of the nervous system of malignant tumors. HEINZ HERMANN has summarized previous reports on the relationship on the nervous system to the tumor under the title of "Nerv und Tumor" in his book "Pathologische Histologie des Peripheren Vegetativen Nerven System". And the following principles are outstanding:

GREEN, MARSHALL et al. first denied the existence of nervous system in tumors. TSUNODA stated that malignant tumor has no relationship to nervous elements, based on his study of nervous system in spontaneous and experimental tumor.

MORELLI, JOUNG, JULIUS, GOLDBERG et al, reported hyperplastic development of nervous system in tumors and stated that tumors are innervated by abundant nervous plexuses which are produced in parallel to the growth of tumor. JULIUS and GOLDBERG stated "The metabolic products of tumor stimulate the production of nervous system in tumor". CAVAZZANA and CEVESE stated that the majority of nerve fibers in tumor are new products which innervate the vascular and nutritional structure of the tumor.

Many writers agree on the point of direct innervation of tumor cells. OERTEL discovered the nerve endings both within and outside of primary malignant tumor and its metastasis. MUEHLMAN and KUBABALIEN stated that cancer is innervated by a nervous system independent from its neighbouring tissues, this nervous system having nerve fibers that terminate at nuclei or nucleoli of the tumor cells. According to CALLIAU cancer has its own ganglion cells, and nerve fibers which run along vessels in tumor. These are the new products which developed in proportion to the growth of the tumor. Therefore, the number of nerve fibers in tumor is greater than in the normal organ and the increment of the fibers is parallel to the malignancy of the tumor.

On the other hand LEUKE and ZAHN et al. denied the new growth of nervous elements of tumor and imputed the nerve fibers present in tumor to be the originally existing nerves. LAZZARINI and OCHOTERNA accepted a productive process of nerve fibers in the precancerous stage of tumor and described how the intensive development of nervous system in tumor disappears in accordance with the gradual destructive mechanism of the tumor. HERZOG agrees with this opinion to the point of destruction of nervous system parallel to the destructive process of tumor itself, but he also discovered the production of nervous system of tumors in rare cases. JABONERO and BORDALLO stated in the report of rectal cancer that "A slight variation is noted in situation, shape, structure and chromasia of nervous plasmabundle in tumor regions where no inflammatory process is found, but in cases where inflammation or edema is present a marked productive process of a nervous terminal network can be observed. When tumor cells proliferate to the nerve cells or nerve fibers of a nerve plexus the fibrinous framework of the nerve cells is markedly involved and the nucleous shadows pyknosis. In every case the amount of nervous tissue of the tumor is not greater than in normal tissue, and the nerve fibers which

are seen there are the preexistent nerve fibers, not the result of hyperplastic growth".

From the summary of this book, as stated above, the various writers show divergent opinions and no common agreement on the nervous system of tumor has been found. With references to these various reports a brief discussion of the microscopic observation of nervous system of YOSHIDA sarcoma in this present study follows.

It has been clearly demonstrated that there are nervous tissues in tissues or organs invaded by tumor cells of YOSHIDA sarcoma, and some of these nervous tissues are distinctly different from the normal picture probably due to the tumor infiltration.

It is an important problem whether the nervous tissues in tumor are new tissues developed parallel with the growth or are the degenerative product of preexistent nervous tissues which ultimately disappear. Under the microscope it is easy to distinguish between nervous tissues in a productive phase or in a degenerative phase, but the most careful observation of nervous tissues in YOSHIDA sarcoma failed to demonstrate the presence of new production of nerves. On the contrary a clear-cut degeneration of preexistent nerves has been proved. In other words, degeneration of preexistent nervous tissues is the rule in cases of YOSHIDA sarcoma and this conclusion agrees with the opinions of HERZOG, JAEONERO and BORDALLO. The new production theory of nervous tissues in tumor is not demonstrated in this study on YOSHIDA sarcoma.

The grade of degeneration in this case is dependent on the grade of tumor infiltration in the tissues or organs, i. e. in such severely infiltrated areas as intestine, liver hilum, abdominal wall, retroperitoneal muscles, renal plexus or spermatic duct in the ascites type of tumor and pulmonary hilum in the subcutaneous type of tumor the nervous apparatus of these organs is markedly destroyed, but in such slightly infiltrated areas as the pulmonary hilum of the ascites type only slight swelling and change of chromasia of nervous apparatus is observed. The nervous syncytium which is the end structure of autonomic nervous systems is more severely affected by tumor infiltration than nerve fibers or ganglion cells. This is destroyed and disappears in the early stage of tumor infiltration. The nervous syncytium is abundant in normal animals and in submucous tissues of bronchi and stomach of tumor-implanted animals where no invasion of tumor is observed, but it is rarely seen in severely invaded tissues. The only exception is observed in submucous tissues of the small intestine which is slightly invaded by tumor cells a little nervous syncytium shows granular degeneration.

Generally speaking, degeneration of nerves is intensive where the tumor infiltration is marked and is slight where the infiltration is mild. But as exceptions, some of the nerve fibers in adrenal cortex and renal interlobar nerves are degenerated despite the absence of tumor infiltration in the surrounding regions. This is probably due to marked degeneration of the renal plexus proximal to these nerves. But these exceptions are quite rare in YOSHIDA sarcoma and in most cases the peripheral nerve fibers in kindney are essentially even though the central part is severely degenerated. The same finding is observed in liver. This is a particular finding

differing from a systematic degenerative process seen in experimental neurotomy and it is probably due to expiring of rats prior to the appearance of secondary morphological degeneration of peripheral nerves following the degeneration of hilar nerves of liver or kidney, due to rapid advance of the disease of tumor-implanted animals.

Next, it is important to discuss whether the degenerative pattern in YOSHIDA sarcoma is characteristic of YOSHIDA sarcoma or is a common degenerative mechanism. In a comparative experiment of nervous degeneration, between YOSHIDA sarcoma and neurotomy or drug injection in nerve, the degenerative pattern of nerves in YOSHIDA sarcoma is quite similar to that of a comparable stage in experimental neurotomy or drug injections. For instance, the nervous degenerative pattern of the portal fissure in the ascites type (Fig. 21, 22) and pulmonary hilum in the subcutaneous type (Fig. 2, 3) caused by tumor infiltration is in general similar to that 6 or 8 days after neurotomy or drug injection. (Fig. 55, 56, 57, 58) (This is the maximum stage of experimental degeneration.) And in the pulmonary hilum in the ascites type where the tumor infiltration is mild, a slight swelling and change in chromasia of nerve fibers (Fig. 1) is observed and this is also similar to that in the early stage (1 or 2 days) of the experimental degeneration. (Fig. 51, 52) Thus, it is impossible to say that degenerative pattern of nerves in YOSHIDA sarcoma is specific for YOSHIDA sarcoma itself. Rather, it appears to be a nonspecific degeneration without relation to cause of degeneration. An exception to this is found in abdominal wall (Fig. 28, 29) and spermatic duct (Fig. 49) where a fine granular degeneration of axis cylinder, which is not observed in the experimental degeneration, is noted. However, this is found in few cases and it is difficult to attribute this to a unique degeneration of YOSHIDA sarcoma. It may possibly be due to variations in experimental conditions.

It is impossible to make a rigid comparison of hourly process of nervous degeneration between YOSHIDA sarcoma and neurotomy or drug injection test, because it is impossible to know the exact time that tumor cells affect the nerve. But it is suspected that the rate of degeneration in YOSHIDA sarcoma is faster than in experimental degeneration, because the interval between beginning of affect of sarcoma cells on nerves and the death of animals is considered to be a few days.

A final observation about the mechanism of nervous degeneration in YOSHIDA sarcoma is presented here. It is impossible to think of the mechanical compression by massive tumor as the reason for this nerve degeneration because the region of tumor infiltration consists of a soft thickening of tissue but never forms a hard tumor mass. In addition, the rapidity of degeneration is thought to be faster in YOSHIDA sarcoma than in experimental neurotomy. Therefore it is difficult to attribute the nutritional disturbance of nerves to simple mechanical compression as the principal mechanism of nervous degeneration. Then it is probable that YOSHIDA sarcoma may produce a chemical substance that acts as a nerve toxin.

In summary the principal neuropathological finding in YOSHIDA sarcoma is a degeneration but never a generation. But this cannot be considered as a specific

concept of neuropathology in malignant tumor, as a result of these simple short-period observations, because the clinical prorocess of malignant tumor is usually much longer than the period of this observation. For example, there was no sign of generation of nervous tissues in YOSHIDA sarcoma. This may be due to the short life span of the tumor-implanted rat, (8 or 12 days in ascites type, 15 or 30 days in subcutaneous type), and especially to the even shorter period between invasion of the nervous system and death of the animals. So it cannot be concluded that there is no generation of nervous tissues in malignant tumor.

Finally, however, the author believes that helpful information in solving the problem of nervous of malignant tumor has been obtained.

V. CONCLUSION

Using SETO's variation of BIELSCHOWSKY's impregnating method for axis-cylinder and EHRLICH's method for myelin sheath, a study of nerve tissues invaded by tumor cell infiltration of YOSHIDA sarcoma and a comparative study of these invaded nerve tissues with experimental degeneration of nerves caused by neurotomy or drug injection was carried out.

Following are the results:

1) In tissues or organs invaded by tumor infiltration of YOSHIDA sarcoma there is some nerve tissue present, but the amount is less than normal.

2) The nerve tissues are clearly degenerated by tumor infiltration and the degree is parallel to the degree of infiltration. There is no sign of generation in the nerve tissues.

3) The nerve syncytium is most profoundly affected by tumor infiltration and rapidly disappears, then degeneration of nerve fibers and ganglion cells follows.

4) The pattern of degeneration is not specific for YOSHIDA sarcoma but is similar to that of experimental degeneration.

5) The rapidity of degeneration in tumor is thought to be faster than that of experimental degeneration.

6) It is more logical to attribute the degenerative mechanism to a chemical substance that acts as a nerve toxin than to mechanical compression.

I am greatly indebted to Assist. Prof. Dr. Ch. KIMURA of our clinic for his constant help during the course of this study.

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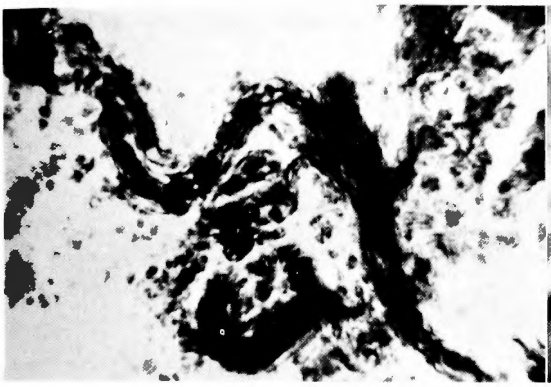

Fig. 1. Degenerated axis-cylinders showing marked swelling. From a nerve running along the bronchia in the lung. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

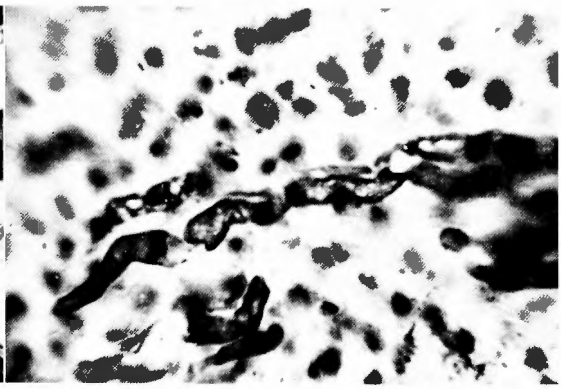

Fig. 2. Degenerated axis-cylinders showing partial swelling, fragmentation and vacuole formation. From a nerve running along the bronchia in the lung. (YOSHIDA sarcoma, Tumor type, B-stain.) ×900

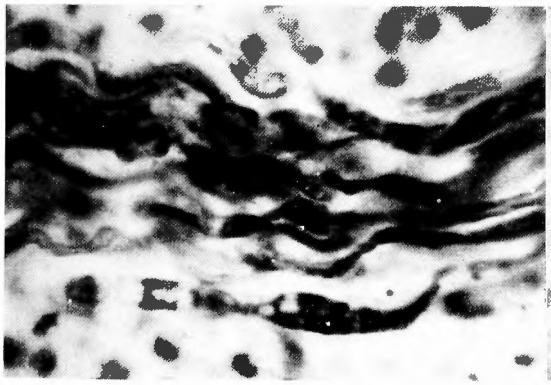

Fig. 3. Degenerated axis-cylinders showing marked swelling with vacuoles. From a nerve along the bronchia in the lung. (YOSHIDA sarcoma, Tumor type, B-stain.) ×900

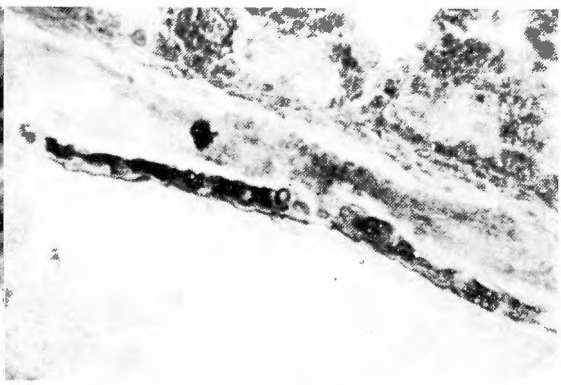

Fig. 4. Degenerated myelin sheath showing partial swelling and fragmentation. From a nerve running along the bronchia in the lung. (YOSHIDA sarcoma, Tumor type, E-stain.) ×400

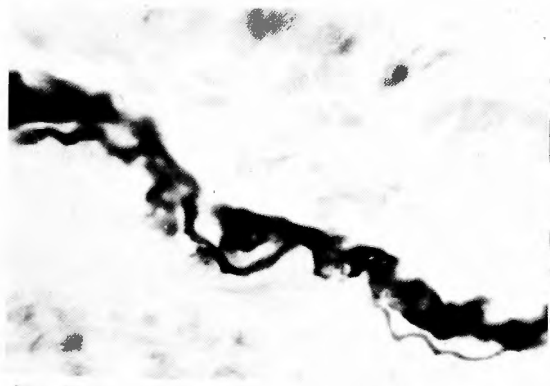

Fig. 5. Degenerated myelin sheath showing swelling with vacuoles. From a nerve running along the bronchia in the lung. (Yoshida sarcoma, Tumor type, E-stain.) ×900

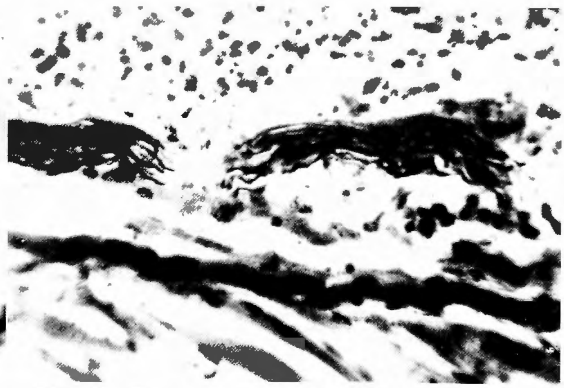

Fig. 6. Degeneration of nerve fibers in the ligamentum gastrohepaticum. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

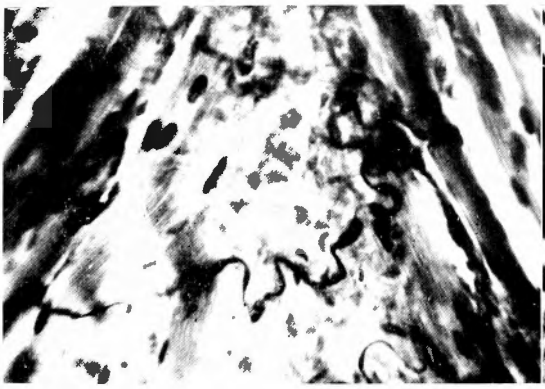

Fig. 7. Flask-like deformation of axis-cylinder in the gastric AUERBACH'S plexus. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

Fig. 8. Normal ganglion cells and nerve fiber in gastric AUERBACH'S plexus. (YOSHIDA sarcoma, Ascites type, B-stain) ×400

Fig. 9. Normal "Schlaengende Territorie" in the submucous layer of the stomach. (YOSHIDA sarcoma, Ascites type, B-stain.) ×900

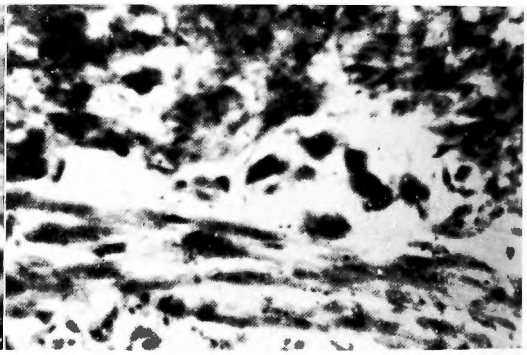

Fig. 10. Degenerated ganglion cells showing marked atrophy. From AUERBACH'S plexus of small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

Fig. 11. Degenerated ganglion cell showing vacuole formation. From AUERBACH'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) ×1500

Fig. 12. Degenerated ganglion cells showing atrophy of cytoplasm, loss of axis-cylinder processes and pyknosis. From AUERBACH'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) ×1000

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Fig. 13. Degenerated ganglion cells showing atrophia of cytoplasm and pyknosis of nuclei. From AUERBACH'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) × 1000

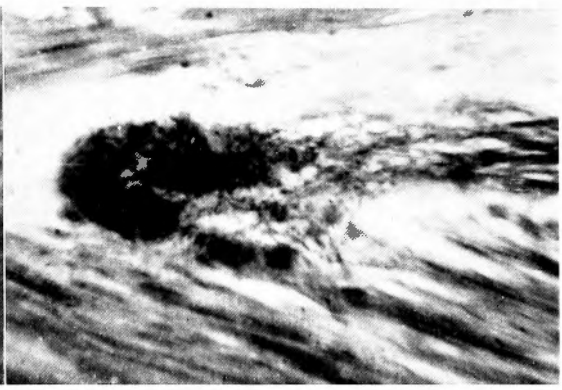

Fig. 14. Granular degeneration of the nerve fibers in AUERBACH'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) × 400

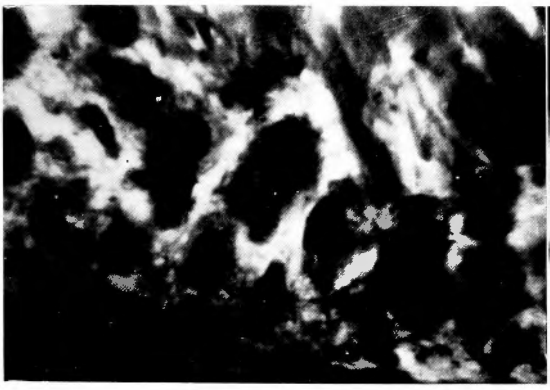

Fig. 15. Degenerated ganglion cells and nerve fibers in AUERBACH'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) × 1000

Fig. 16. Degenerated ganglion cells showing atrophy of cytoplasm, loss of axis-cylinders and pyknosis of nuclei. From MEISSNER'S plexus of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) × 1000

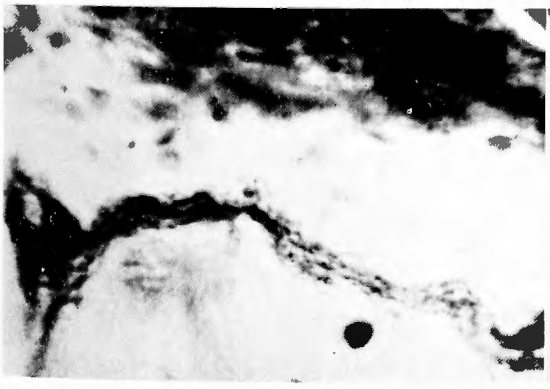

Fig. 17. Granular degeneration of nervous syncytium in the submucous layer of the small intestine. (Yoshida sarcoma, Ascites type, B-stain.) × 1000

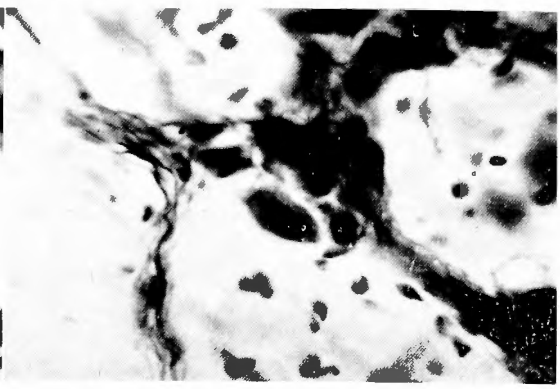

Fig. 18. Normal nerve plexus in the subserous layer of the small intestine. (YOSHIDA sarcoma, Ascites type, B-stain.) × 1000

Fig. 19. Deformation of cytoplasm and nuclear pyknosis of ganglion cells in AUERBACH'S plexus of rectum. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

Fig. 20. Degenerated ganglion cells showing atrophy of cytoplasm and loss of axsis-cylinder processes. From AUERBACH'S plexus of the rectum. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

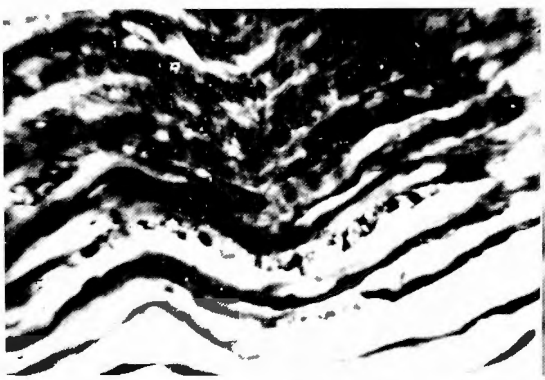

Fig. 21. Degenerated nerve fibers showing swelling, fragmentation and vacuole formation. From nerve bundles of the portal fissure. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

Fig. 22. Degenerated myelin sheaths showing marked swelling and fragmentation involving many vacuoles. From nerve bundle of the portal fissure. (YOSHIDA sarcoma, Ascites type, B-stain,) ×1000

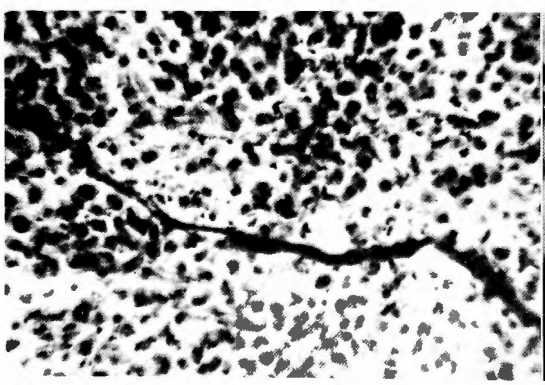

Fig. 23. Degenerated nerve fibers in GLISSON'S capsule showing swelling of axis-cylinder. From a nerve in the region of the portal fissure. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

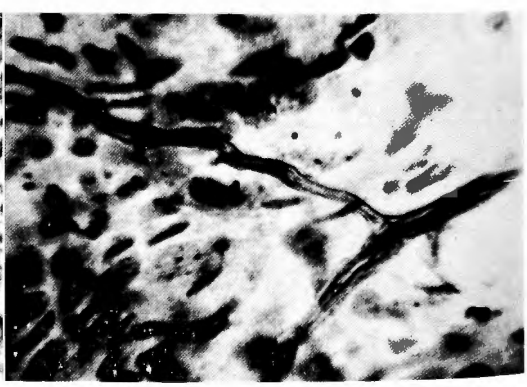

Fig. 24. Normal nerve fibers in GLISSON'S capsule of the liver. (YOSHIDA sarcoma, Ascites type, B-stain.) ×400

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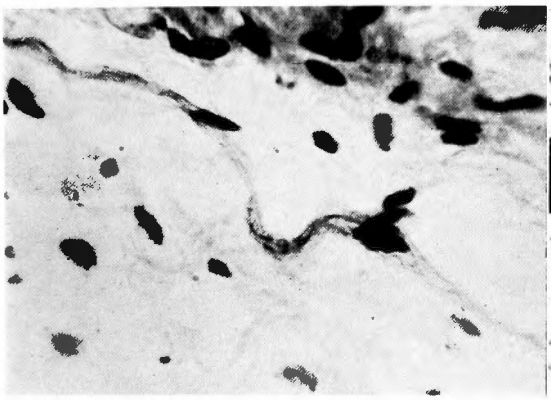

Fig. 25. Normal nerve syncytium in GLISSON's capsule of the liver. (B-stain) ×1000

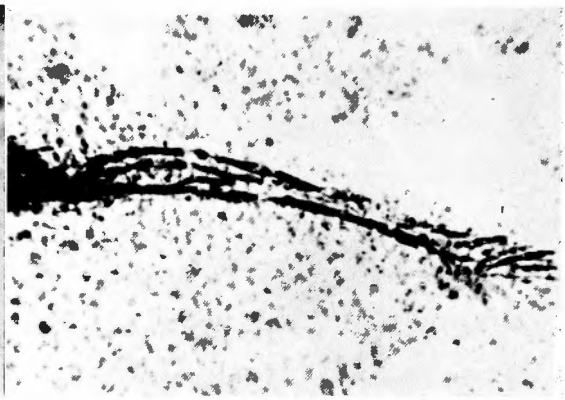

Fig. 26. Degenerated nerve fibers showing partial fragmentation and vacuole formation in the abdomioal wall. (YOSHIDA sarcoma, Ascites type, B-stain.) ×300

Fig. 27. Degenerated myelin sheaths (the same portion as Fig. 26) showing partial swelling and fragmentation with vacuoles. (YOSHIDA sarcoma, Ascites type, E-stain.) ×300

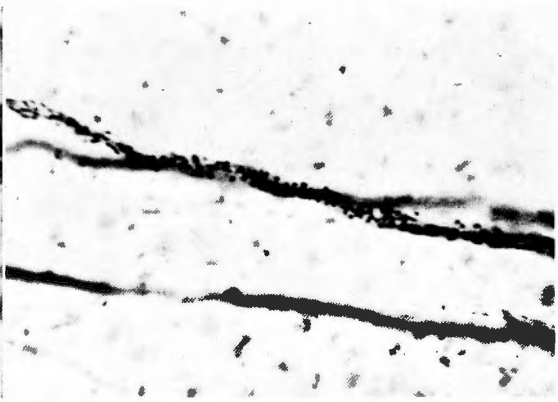

Fig. 28. Fine granular degeneration of nerve fibers in the abdominal wall. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

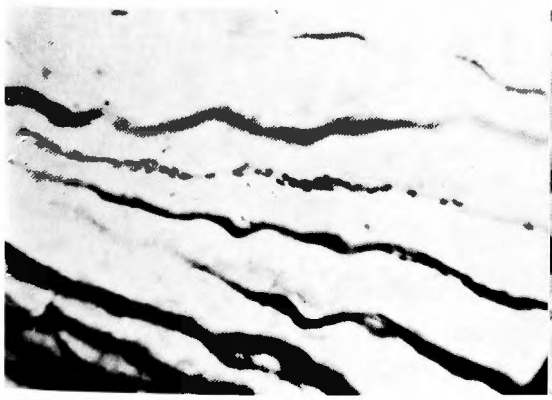

Fig. 29. Fine granular degeneration of nerve fibers in abdominal wall. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

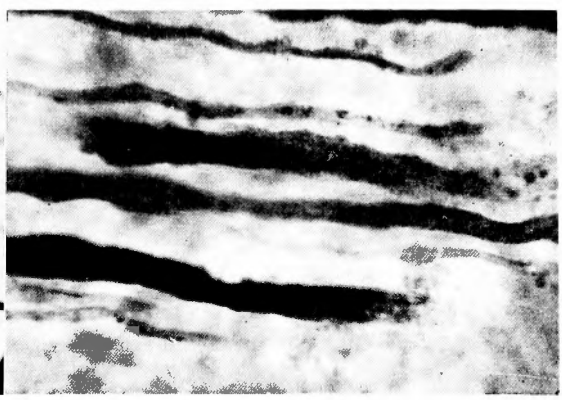

Fig. 30. Degenerated myelin sheaths (the same portion as Fig. 28, 29) showing swelling. (YOSHIDA sarcoma, Ascites type, E-stain.) ×900

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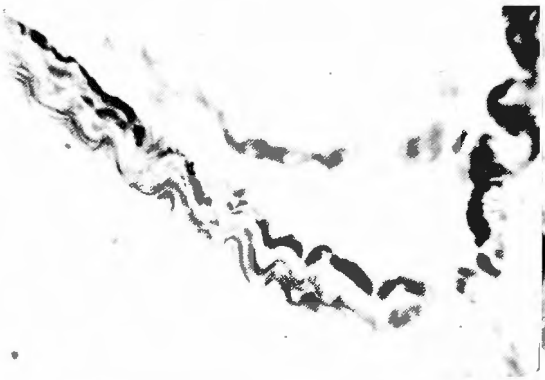

Fig. 31. Granular degenerated nerve fibers showing partial fragmentation with vacuoles in the retroperitoneal muscle. (Yoshida sarcoma, Ascites type, B-stain.) ×300

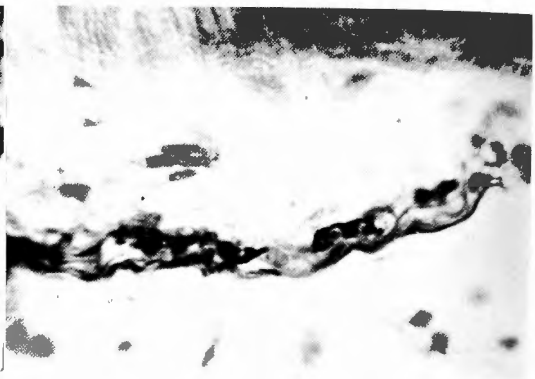

Fig. 32. Granular degenerated nerve fibers in the retroperitoneal muscle. (Yoshida sarcoma, Ascites type, B-stain.) ×600

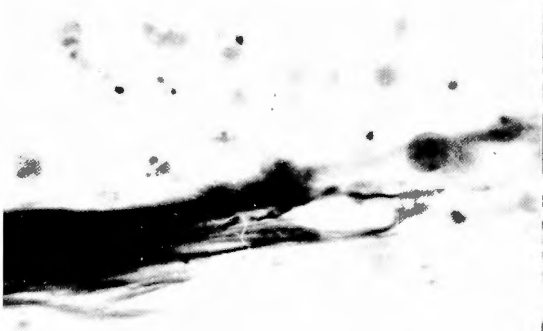

Fig. 33. Granular degenerated nerve fibers in the cortex of the suprarenal gland (Zona fasciculata). (Yoshida sarcoma, Ascites type, B-stain.) ×1000

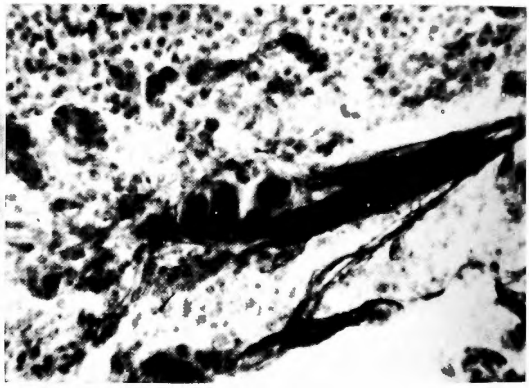

Fig. 34. Normal nerve bundle and ganglion cells in the medulla of the suprarenal gland. (Yoshida sarcoma, Ascites type, B-stain.) ×300

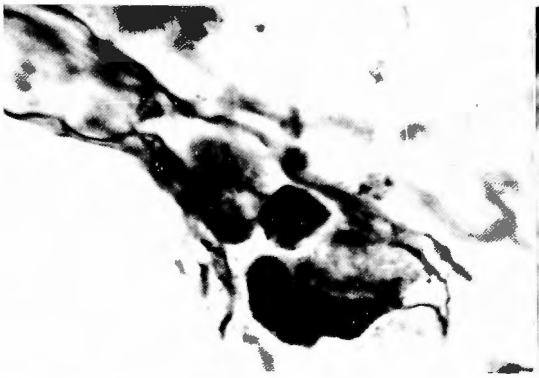

Fig. 35. Normal nerve fibers and chromaffine cells in the medulla of the suprarenal gland. (Yoshida sarcoma, Ascites type, B-stain.) ×1000

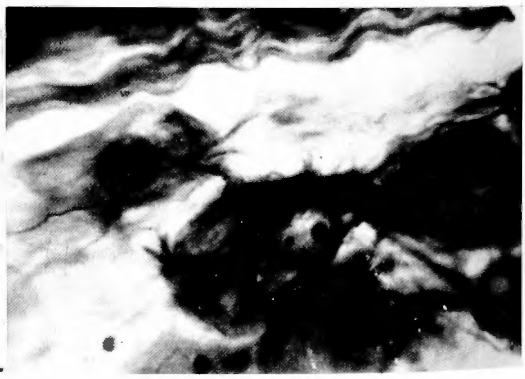

Fig. 36. Degenerated ganglion cells, "Fortsatzdysharmonie", in the renal plexus. (Yoshida sarcoma, Ascites type, B-stain.) ×1500

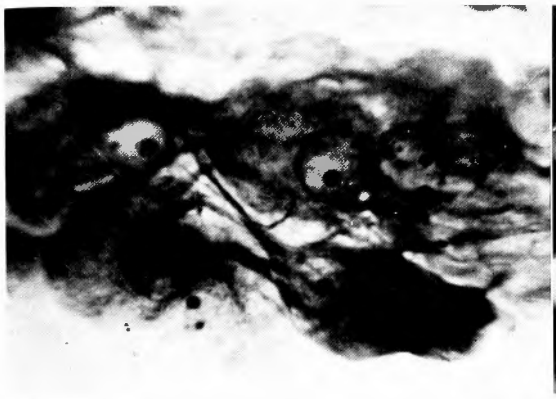

Fig. 37. Degenerated ganglion cell showing "Randstellung der Kern" in renal plexus. (YOSHIDA sarcoma, Ascites type, B-stain.) ×1500

Fig. 38. Degenerated ganglion cells showing "Randstellung der Kern" in renal plexus. (YOSHIDA sarcoma, Ascites type, B-stain.) ×1500

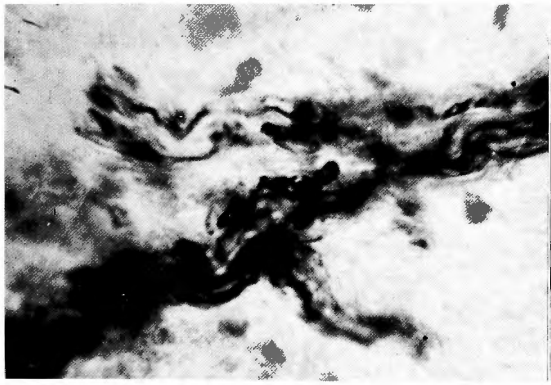

Fig. 39. Degenerated nerve fibers showing fragmentation with vacuole formation in the renal plexus. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

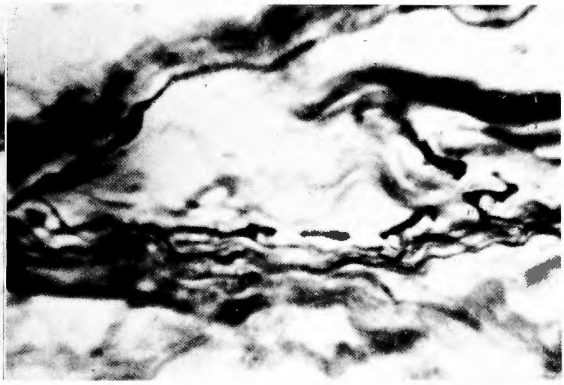

Fig. 40. Degenerated nerve fibers showing partial swelling, fragmentation and vacuole formation in the renal plexus. (YOSHIDA sarcoma, Ascites type, B-stain.) ×300

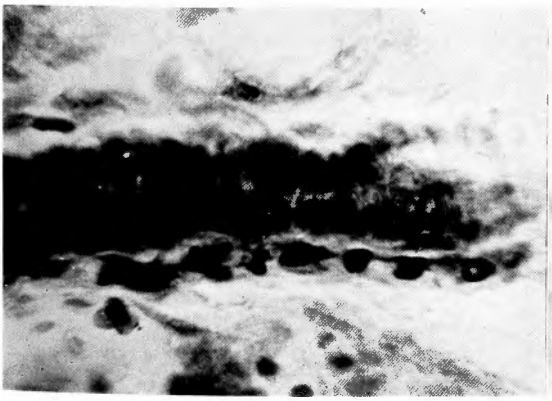

Fig. 41. Degenerated myelin sheaths in renal plexus. (YOSHIDA sarcoma, Ascites type, E-stain.) ×400

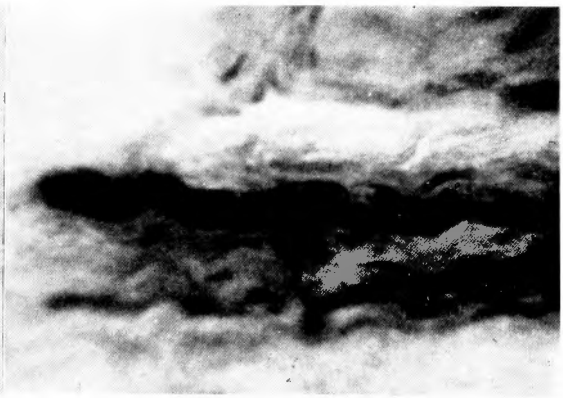

Fig. 42. Degenerated myelin sheaths showing marked swelling and vacuole formation in the renal plexus. (YOSHIDA sarcoma, Ascites type, E-stain.) ×900

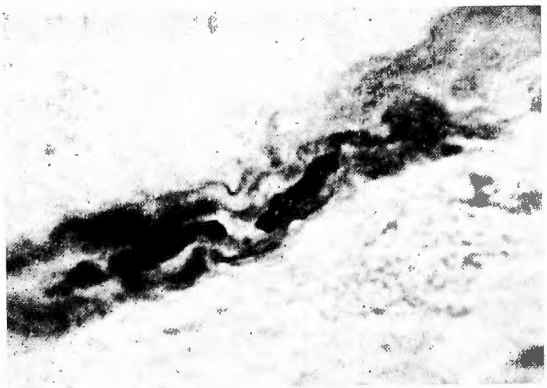

Fig. 43. Granular degeneration of nerve fibers of renal hilum. (Yoshida sarcoma, Ascites type, B-stain,) ×600

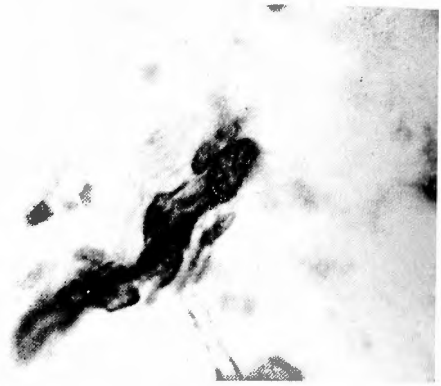

Fig. 44. Degenerated myelin sheaths showing swelling, partial fragmentation and vacuole formation. From nerve in the renal hilus. (Yoshida sarcoma, Ascites type, E-stain.) ×900

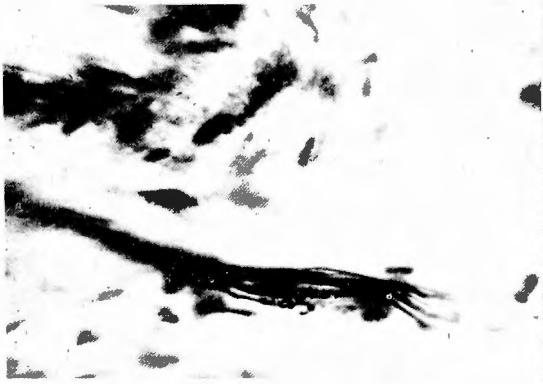

Fig. 45. Granular degeneration of the nerve fibers running along interlobar artery in the kidney. (Yoshida sarcoma, Ascites type, B-stain.) ×400

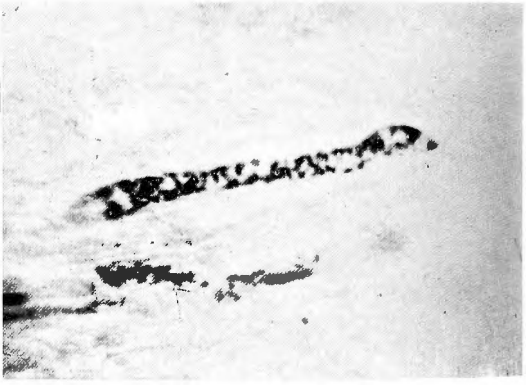

Fig. 46. Granular degeneration of nerve fibers in the submucous layer of the pelvis renalis. (Yoshida sarcoma, Tumor type, B-stain.) ×600

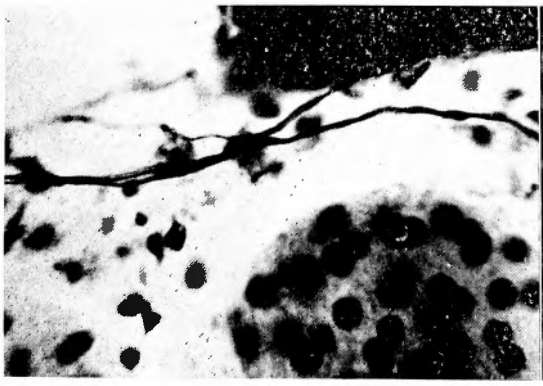

Fig. 47. Normal nerve fibers running along the interlobular artery in the kidney. (Yoshida sarcoma, Ascites type, B-stain.) ×600

Fig. 48. Normal nerve syncytium in the submucous layer of the pelvis renalis. (B-stain) ×1000

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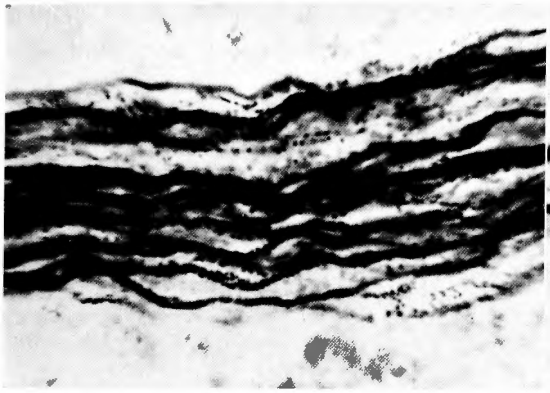

Fig. 49. Fine granular degeneration of nerve bundle running along the spermatic duct. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

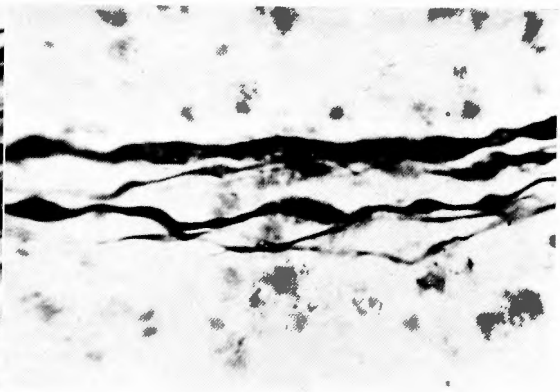

Fig. 50. Degenerated nerve fibers showing swelling with vacuole formation. From the nerve running along the spermatic duct. (YOSHIDA sarcoma, Ascites type, B-stain.) ×600

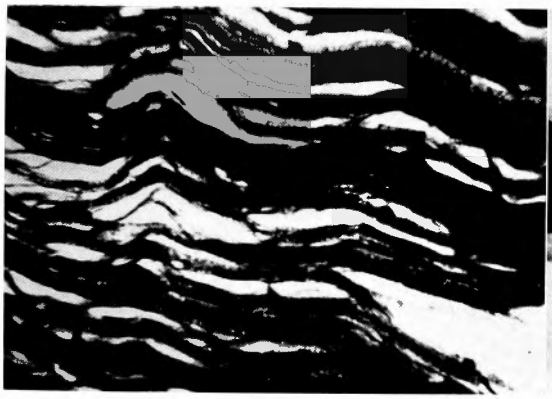

Fig. 51. Degenerated nerve fibers of ischiatic nerve, 2 days after neurotomy. (B-stain) ×300

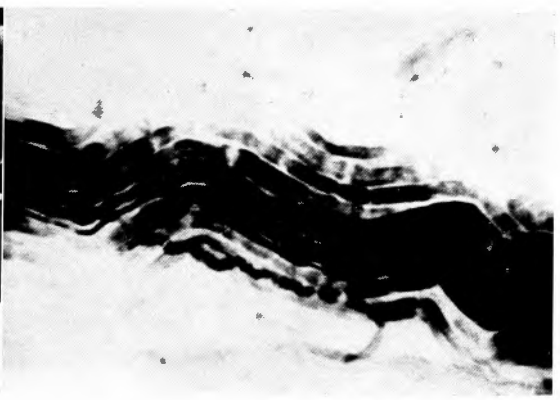

Fig. 52. Degenerated myelin sheaths of ischiatic nerve, 2 days after neurotrmy. (E-stain.) ×300

Fig. 53. Degenerated nerve fibers of ischiatic nerve, 4 days after neurotomy. (B-stain.) ×300

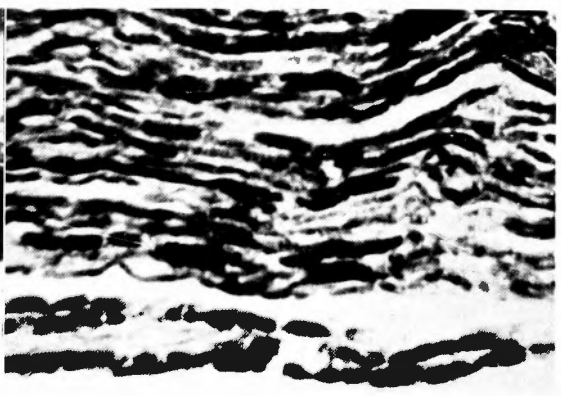

Fig. 54. Degenerated myelin sheaths of ischiatic nerve, 4 days after neurotomy. (E-stain.) ×300

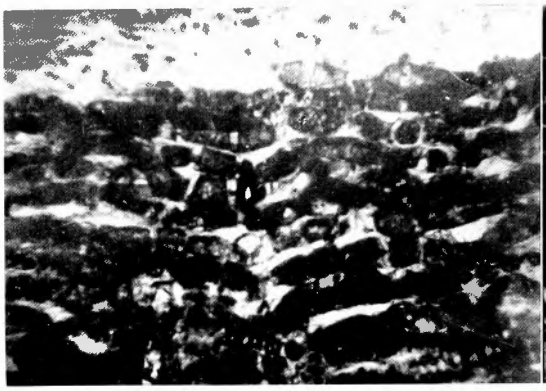

Fig. 55. Degenerated nerve fibers of ischiatic nerve, 6 days after neurotomy. (B-stain.)
×300

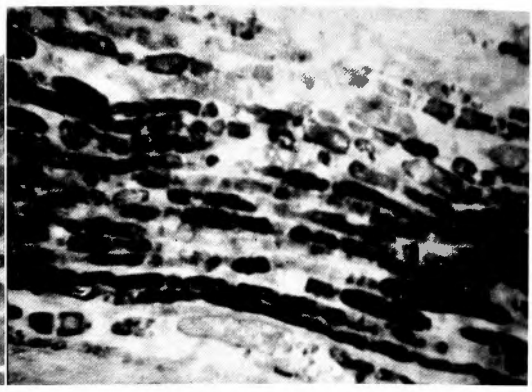

Fig. 56. Degenerated myelin sheaths of ischiatic nerve, 6 days after neurotomy. (E-stain,)
×300

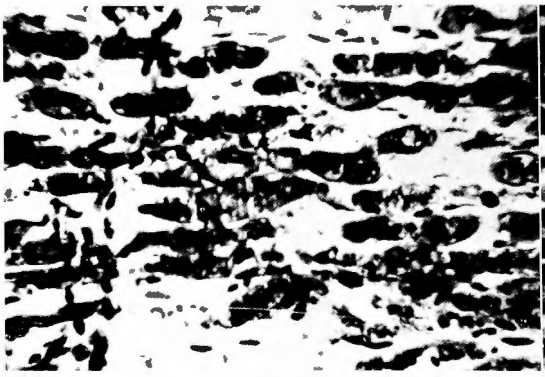

Fig. 57. Degenerated nerve fibers of ischiatic nerve, 8 days after neurotomy. (B-stain)
×300

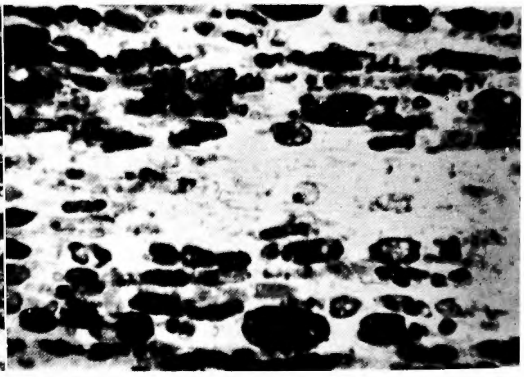

Fig. 58. Degenerated myelin sheaths of ishiatic nerve, 8 days after neurotomy. (E-stain)
×300

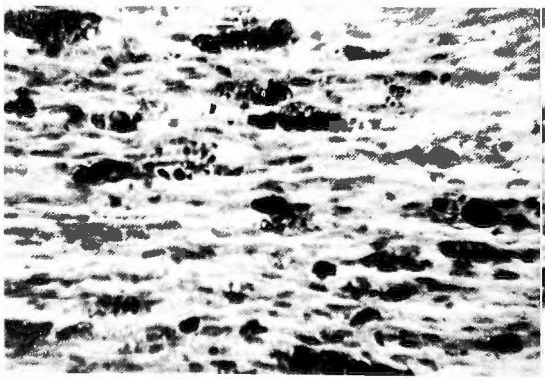

Fig. 59. Degenerated nerve fibers of ischiatic nerve, 14 days after neurotomy. (B-stain)
×300

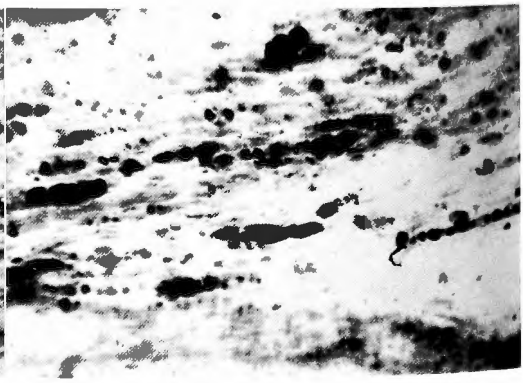

Fig. 60. Degenerated myelin sheaths of ischiatic nerve, 14 days after neurotomy. (E-stain)
×300

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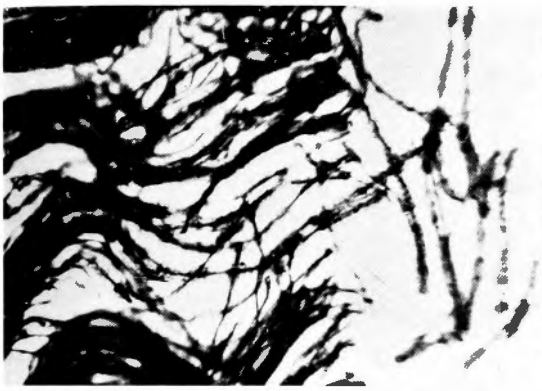

Fig. 61. Degenerated nerve fibers of ischiatic nerve, 4 days after alcohol injection. (B-stain) ×300

Fig. 62. Degenerated nerve fibers of ischiatic nerve, 8 days after alcohol injection. (E-stain) ×300

Fig. 63. Degenerated nerve fibers of ischiatic nerve, 14 days after alcohol injection. (B-stain) ×300

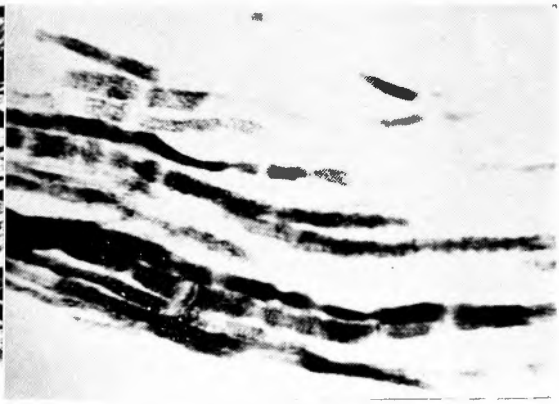

Fig. 64. Degenerated myelin sheaths of ischiatic nerve, 4 days after phenol injection. (E-stain) ×300

Fig. 65. Degenerated myelin sheaths of ischiatic nerve, 8 days after phenol injection. (E-stain) ×300

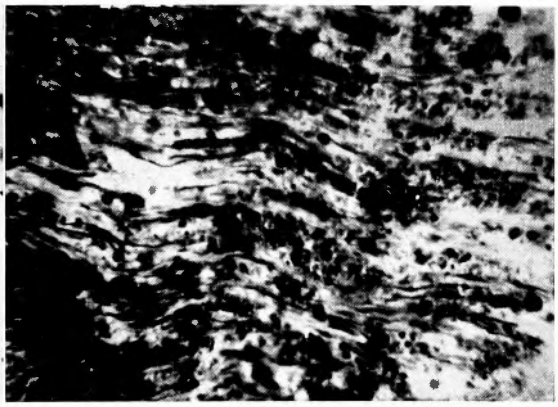

Fig. 66. Degenerated myelin sheaths of ischiatic nerve, 14 days after phenol injection. (E-stain) ×300

EXPLANATION OF FIGURES

1) B-stain: Seto's variation of Bielschowsky's silver staining.
2) E-stain: Ehrlich's acid hematoxylin method.

M. Hakoda

和文抄録

吉田肉腫に於ける神経病理学的研究

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福井県小浜市民病院外科（医長：佐藤博正博士）

箱田允昭

Bielschowsky 氏神経軸索鍍銀法の瀬戸氏変法及び Ehrlich 氏神経髄鞘染色法を用いて，吉田肉腫に於て腫瘍細胞の浸潤を受けた組織及び器管に於ける神経組織の態度を観察し，これを対照健常試獣の神経，及び切断及び薬液注射（アルコール，フェノール）による変性神経と比較して次の結論を得た．

1） 吉田肉腫に於ては腫瘍細胞の浸潤した組織及び器管にも神経組織は存在するが，その数は正常に比べて決して多くない．

2） 神経組織は腫瘍細胞の浸潤により明らかに変化を受け，その変化の程度は大体に於て浸潤の程度に比例する．而してこれらの変化は退行変性が主体であり，神経の新生及び増殖性の変化は否定出来る．

3） 腫瘍細胞の浸潤により Nervöse Syncytium が最も強く影響を受けて早期に消失し，次いで神経細胞及び神経線維が変性を起す．

4） 吉田肉腫に於ける神経変性像は吉田肉腫特有のものでなく，切断及び薬液注射による変性実験に於ける変性像と大差は認められない．

5） 吉田肉腫に於ける神経変性速度は変性実験の変性速度よりむしろ早いものと推測される．

6） 吉田肉腫に於ける神経の変性機転は機械的圧迫より神経毒によるものと考えるのが妥当である．